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17FEB03 E785218-1 D01030
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1. Your reference	MG/PMS/PB60065
2. Patent application number *(The Patent Office will fill in his part)*	0303467.5 14 FEB 2003
3. Full name, address and postcode of the or of each applicant *(underline all surnames)* Patents ADP number *(if you know it)* If the applicant is a corporate body, give the country/state of its incorporation	Glaxo Group Limited Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, Great Britain 473587003 United Kingdom
4. Title of the invention	Novel Compounds
5. Name of your agent *(if you have one)* "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)* Patents ADP number *(if you know it)* 8072555006	Corporate Intellectual Property GlaxoSmithKline Corporate Intellectual Property (CN9 25.1) 980 Great West Road BRENTFORD Middlesex TW8 9GS
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number	Country / Priority application number *(if you know it)* / Date of filing *(day / month / year)*
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application / Date of filing *(day / month / year)*
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is named as an applicant, or c) any named applicant is a corporate body. See note (d)*	

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Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature M Gibson Date 14-Feb-03

12. Name and daytime telephone number of person to contact in the United Kingdom: M Gibson 01279 644841

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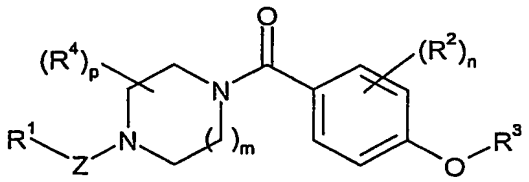
NOVEL COMPOUNDS

The present invention relates to novel piperazine and diazepane benzamide derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

WO 02/76925 (Eli Lilly), WO 00/06254 (Societe Civile Bioprojet), WO 01/66534 (Abbott Laboratories) and (WO 03/004480 (Novo Nordisk) describe a series of compounds which are claimed to be histamine H3 antagonists. WO 02/40466 (Ortho McNeill Pharmaceutical) disclose a series of amido-alkyl piperidine and amido-alkyl piperazine derivatives which are claimed to be useful in treatment of various nervous system disorders.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel H3 antagonists such as the current series could be useful for the treatment of cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

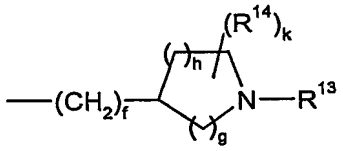
The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents $-C_{1-6}$ alkyl, $-C_{1-6}$ alkylC_{1-6} alkoxy, $-C_{3-8}$ cycloalkyl, aryl, heterocyclyl, heteroaryl, $-C_{1-6}$ alkyl-aryl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, $-C_{1-6}$ alkyl-heteroaryl, $-C_{1-6}$ alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or -heterocyclyl-heterocyclyl;
wherein R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, $-CONR^{15}R^{16}$, $-NR^{15}COR^{16}$, $-NR^{15}SO_2R^{16}$ or $-SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;
Z represents CO or SO_2;
R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;
m is 1 or 2;
n is 0, 1 or 2;
p is 0, 1 or 2;
R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;
R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group selected from pyrrolidine, piperidine and homopiperidine optionally substituted by one or two R^{17} groups;
R^{13} represents C_{1-6} alkyl, C_{3-6} cycloalkyl or $-C_{1-4}$ alkyl-C_{3-6} cycloalkyl;
R^{14} and R^{17} independently represent halogen, C_{1-4} alkyl, haloC_{1-6} alkyl, OH, diC_{1-6} alkylamino or C_{1-6} alkoxy;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
R^4 represents C_{1-6} alkyl such that when p represents 2, said R^4 groups may form a bridging group consisting of one or two methylene groups;
or a solvate thereof.

~~Specific compounds of formula (I) which may be mentioned are those wherein R^1 is~~ linked to Z via a carbon atom and m represents 1 and Z represents CO.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term "aryl" includes single and fused rings wherein at least one ring is aromatic, for example, phenyl, naphthyl and tetrahydronaphthalenyl.

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring containing 1 to 3 heteroatoms selected from oxygen or nitrogen. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, diazepanyl, tetrahydrofuranyl, tetrahydropyranyl and azepanyl.

The term "heteroaryl" is intended to mean a 5-6 membered monocyclic aromatic or a fused 8-10 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl; furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl and pyridyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R^1 represents -C_{1-6} alkyl (eg. i-propyl), C_{3-8} cycloalkyl (eg. cyclohexyl or cycloheptyl), aryl (eg. phenyl or tetrahydronaphthalene), heteroaryl (eg. furyl, thienyl, pyridyl, quinoxaline, pyrazine, 1,2,3-benzothiadiazole, isoxazole or pyrazole), heterocyclyl (eg. morpholine, pyrrolidine, tetrahydrofuran or tetrahydropyran) or -C_{1-6} alkyl-aryl (eg. α-methylbenzyl or α,α-dimethylbenzyl).
Preferably, R^1 is optionally substituted by one or more (eg. 1, 2 or 3) halogen (eg. chlorine), cyano, trifluoromethyl, C_{1-6} alkyl (eg. methyl or t-butyl), $MeSO_2$- or N-propyl$_2SO_2$- groups.
More preferably, R^1 represents C_{3-8} cycloalkyl (eg. cyclohexyl), heteroaryl (eg. furyl) or aryl (eg. phenyl or tetrahydronaphthalene) optionally substituted by a cyano group.
Preferably, Z represents CO.
Preferably, p represents 0 or 2, more preferably 0.
When p represents 2, both R^4 groups are preferably methyl or form a methylene bridging group.

Preferably, m represents 1.

Preferably, n represents 0.

Preferably, R^3 represents $-(CH_2)_q-NR^{11}R^{12}$.

Preferably, q represents 3.

Preferably, $NR^{11}R^{12}$ represents an N-linked heterocyclic group, more preferably unsubstituted piperidine.

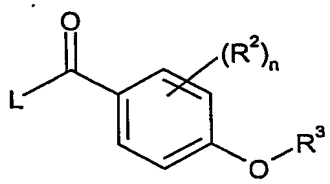
Preferred compounds according to the invention include examples E1-E46 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

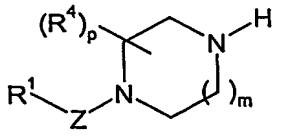
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)



(II)

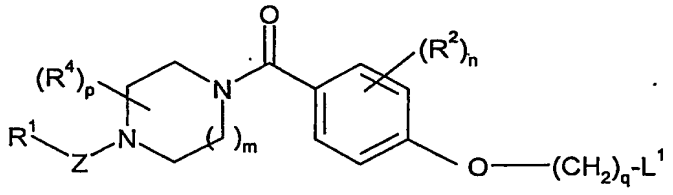
with a compound of formula (III)



(III)

or a protected derivative thereof, wherein R^1, Z, R^2, R^3, R^4, m, n and p are as defined above and L represents a suitable leaving group, such as a halogen atom such as chlorine or a hydroxy group which may be converted into a leaving group; or

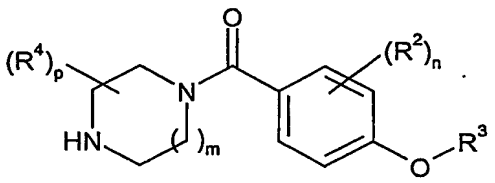
(b) preparing a compound of formula (I) wherein R^3 represents $(CH_2)_q NR^{11}R^{12}$ which comprises reacting a compound of formula (IV)



(IV)

wherein R^1, Z, R^2, R^4, m, n, p and q are as defined above and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine) with a compound of formula $HNR^{11a}R^{12a}$; wherein R^{11a} and R^{12a} are as defined above for R^{11} and R^{12} or a group convertible thereto; or

(c) reacting a compound of formula (V)



(V)

or a protected derivative thereof, wherein R^2, R^3, R^4, m, n and p are as defined above, with a compound of formula R^{1a}-Z-L^2, wherein R^{1a} is as defined above for R^1 or a group convertible thereto, Z is as defined above and L^2 represents a suitable leaving group, such as a halogen atom (eg. chlorine) or a hydroxy group which may be converted into a suitable leaving group; and optionally thereafter

(d) deprotecting a compound of formula (I) or converting groups which are protected; and optionally thereafter

(e) interconversion to other compounds of formula (I).

Process (a) typically comprises halogenation of the compound of formula (II) with a suitable halogenating agent (eg. thionyl chloride) followed by reaction with the compound of formula (III) in the presence of a suitable base such as triethylamine or a solid supported base such as diethylaminomethylpolystyrene in a suitable solvent such as dichloromethane. Process (a) may also typically comprise activation of the compound of formula (II) with a coupling reagent such as dicyclohexylcarbodiimide or solid supported carbodiimide in a suitable solvent such as N,N-dimethylformamide followed by reaction with the compound of formula (III).

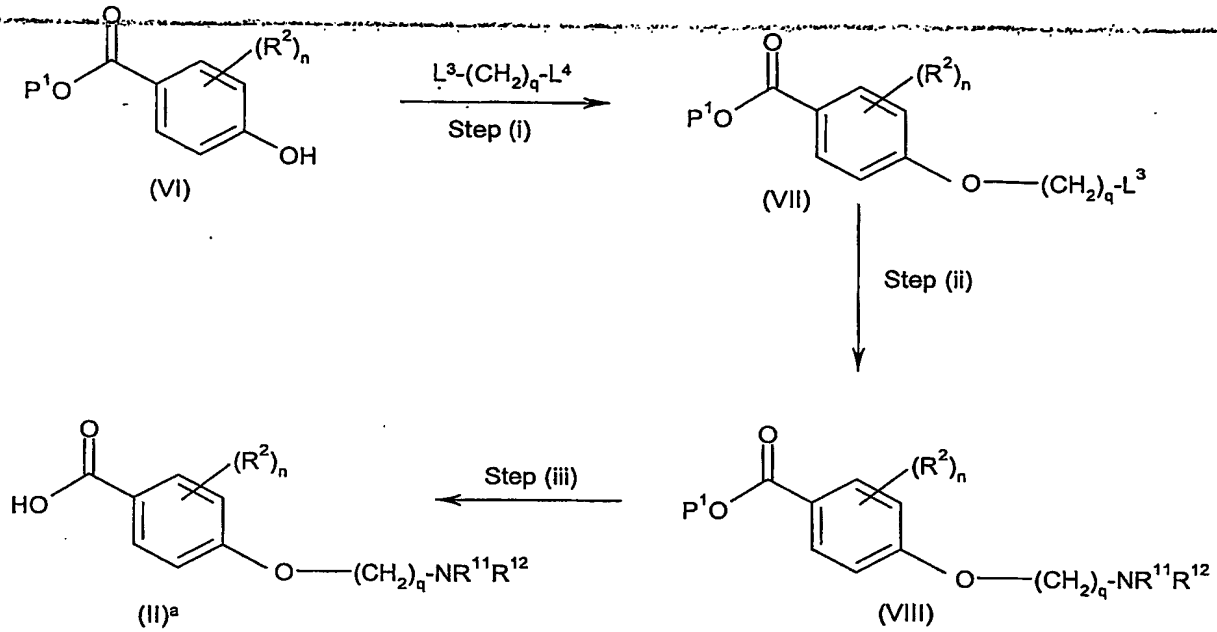
Process (b) is typically performed in the presence of a suitable solvent (such as 1-butanol) at an elevated temperature.

Process (c) typically comprises the use of a suitable base, such as triethylamine or a solid supported base such as diethylaminomethylpolystyrene in a suitable solvent such as dichloromethane. Process (c) may also involve activation of a carboxylic acid with a suitable coupling agent such as dicyclohexylcarbodiimide followed by reaction with the compound of formula (V).

In process (d), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl ($-COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (e) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis or amide bond formation.

Compounds of formula (II) wherein R^3 represents $-(CH_2)_q-NR^{11}R^{12}$ may be prepared in accordance with the following procedure:



wherein R^2, n, q, R^{11} and R^{12} are as defined above, P^1 represents a protecting group such as methyl, ethyl or t-butyl, L^3 and L^4 independently represent a leaving group such as halogen (eg. L^3 represents chlorine and L^4 represents bromine). The $-CO_2H$ group of compounds of formula $(II)^a$ may be converted to -COL wherein L represents a leaving group by, for example, halogenation using thionyl chloride.

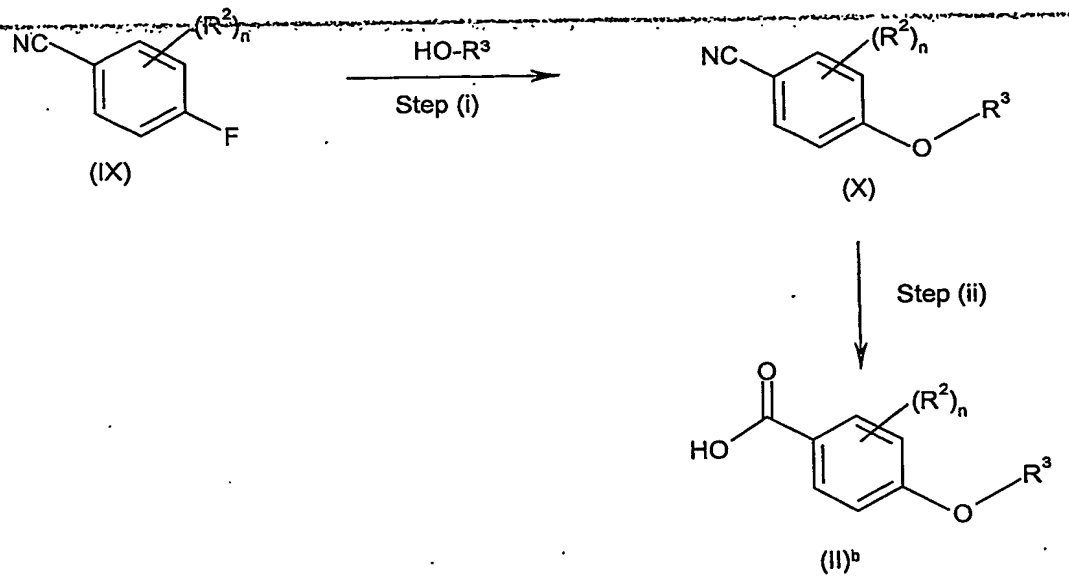
Step (i) typically comprises reaction of a compound of formula (VI) with a suitable alkylating agent such as 1-bromo-3-chloropropane in a suitable solvent such as acetone in the presence of potassium carbonate.

Step (ii) typically comprises treatment of a compound of formula (VII) with an amine of formula $HNR^{11}R^{12}$.

Step (iii) comprises a deprotection reaction which may be performed for example under acidic conditions with hydrochloric acid.

Compounds of formula (IV) may be prepared by hydrolysing a compound of formula (VII) as defined above under suitable conditions (eg. under acidic conditions with HCl), followed by suitable activation (eg. by conversion into the acid chloride with thionyl chloride), and then treatment with a compound of formula (III) as defined above.

Compounds of formula (II) may also be prepared in accordance with the following procedure:



(IX) (X) (II)ᵇ

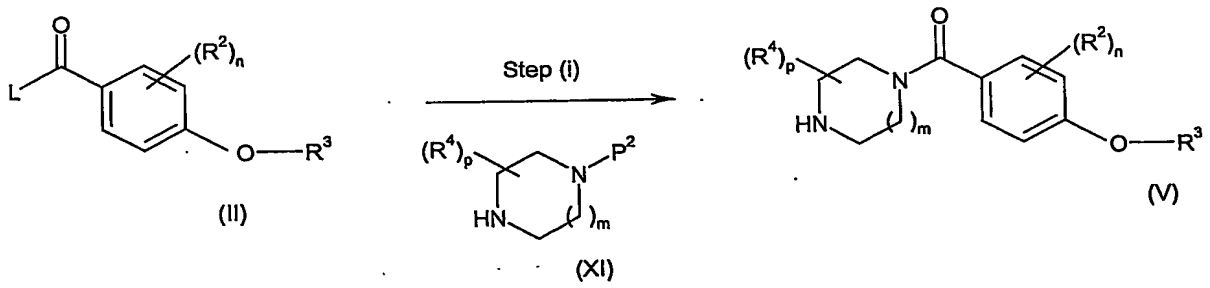
wherein R^2, n and R^3 are as defined above.

Step (i) typically comprises reaction of a compound of formula (IX) in the presence of a suitable base such as sodium hydride in an appropriate solvent such as dimethylsulfoxide or N,N-dimethylformamide.

Step (ii) typically comprises a hydrolysis reaction for example under acidic conditions using hydrochloric acid.

Compounds of formula (IV) may be prepared using an analogous procedure using HO-$(CH_2)_q$-L^4, wherein q is as defined above and L^4 represents an OH group or a group convertible to a leaving group.

Compounds of formula (V) may be prepared in accordance with the following procedure:



(II) (XI) (V)

wherein L, R^2, n, R^3, R^4, m and p are as defined above and P^2 represents a suitable protecting group such as t-butoxycarbonyl (t-Boc) or t-butyl.

Step (i) typically comprises the use of a suitable base such as triethylamine in a suitable solvent such as dichloromethane followed by deprotection under suitable conditions, eg. removal of a t-Boc protecting group with dioxan/hydrochloric acid.

Compounds of formula (III), (VI), (IX) and (XI) are either known in the literature or can be prepared by analogous methods.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive dysfunction, epilepsy, neuropathic pain, inflammatory pain, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia, attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular neurodegenerative disorders including Alzheimer's disease.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000

mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

Ethyl 4-(3-Piperidin-1-ylpropoxy)benzoate (D1)

A stirred mixture of ethyl 4-(3-chloropropoxy)benzoate (4.73g) (D.A.Walsh *et al* J. Med. Chem. 1989, **32**(1), 105), piperidine (2.9ml), sodium carbonate (3.1g) and potassium iodide (162mg) in 1-butanol (50ml) was heated at 105° C for 16h. The reaction was cooled to rt, diluted with EtOAc (100ml), washed with water (3x50ml), saturated brine (50ml), dried ($MgSO_4$) and evaporated to give the title compound (D1) (6.88g). MS electrospray (+ion) 292 (MH^+). ^1H NMR δ ($CDCl_3$): 7.98 (2H, d, J=8.8Hz), 6.90 (2H, d, J=8.8Hz), 4.34 (2H, q ,J=7.5Hz), 4.06 (2H, t, J=6.3Hz), 2.46 (4H, m), 2.00 (2H, m), 1.50 (6H, m), 1.38 (3H, t, J=7.5Hz).

Description 2

4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2)

A solution of ethyl 4-(3-piperidin-1-ylpropoxy)benzoate (D1) (1.4g) in concentrated hydrochloric acid (15ml) was heated under reflux for 1h, cooled and evaporated to give the title compound (D2) (1.02g). MS electrospray (+ion) 264 (MH^+). ^1H NMR δ (DMSO-d6): 10.59 (1H, s), 10.25 (1H, s), 7.90 (2H, d, J=9Hz), 7.02 (2H, d, J=9Hz), 4.14 (2H, t, J=6Hz), 3.05-3.52 (4H, m), 2.91 (2H, m), 2.20 (2H, m), 1.25-1.91 (6H, m).

Description 3

4-(3-Piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3)

4-(3-Piperidin-1-ylpropoxy)benzoic acid hydrochloride (D2) (0.23g) in thionyl chloride (5ml) was heated under reflux for 1h. The reaction mixture was then evaporated to a minimum and co-evaporated from DCM (3 x 10ml) to give the title compound (D3) as a white powder (0.24g).

Description 4

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylpiperazine (D4)

To t-butoxycarbonylpiperazine (5.65g) in DCM (70ml) was added triethylamine (16.2 ml) followed by slow addition of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (10.60g) in DCM (100ml). The reaction was stirred at rt for 3h, then washed with saturated sodium hydrogen carbonate solution (2 x 200ml) followed by brine (100ml). The organic layer was dried ($MgSO_4$) and evaporated to a brown solid which was purified by chromatography [silica gel; 0-6% MeOH (containing 10% 0.880 ammonia solution)/DCM] to give the title compound (D4) as a pale brown solid (12.05g).

Description 5

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5)

To 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylpiperazine (D4) (12.05 g) in DCM (150 ml) was added 4N HCl/Dioxane (35 ml), forming a white precipitate. The reaction was stirred for 2.5 hours before evaporation. The white crude solid was triturated with DCM and dried overnight at 50°C to yield the title compound (D5) (8.26 g).

Description 6

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylhomopiperazine (D6)

To t-butoxycarbonylhomopiperazine (0.76g) in DCM (10ml) was added triethylamine (1.2ml) and the mixture was cooled to 0°C followed by the slow addition of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (1.2g) in DCM (10ml). The mixture was stirred at rt for 3h, then washed with water. The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (D6) as a cream coloured solid (1.69g).

Description 7

1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]homopiperazine dihydrochloride (D7)

To 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]-4-t-butoxycarbonylhomopiperazine (D6) (1.50g) in DCM (20ml) was added 4N HCl (4ml) and the mixture was allowed to stir at rt overnight. Evaporation of solvent followed by drying under high vacuum afforded the title compound (D7) as a white solid (1.5g).

Description 8

(1S,4S)-5-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane-2 carboxylic acid t-butyl ester (D8)

To (1S,4S)-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylic acid t-butyl ester (1.12g) in DCM (10ml) was added triethylamine (1.77ml) and the reaction was cooled to 0°C followed by the slow addition of 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (1.8g) in DCM (10ml). The mixture was stirred at rt for 3h, then washed with water. The organic layer was dried ($MgSO_4$) and evaporated to give the title compound (D8) as a cream coloured solid (2.52g).

Description 9

(1S,4S)-2-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1]heptane dihydrochloride (D9)

To (1S,4S)-5-[4-(3-piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane-2 carboxylic acid tert-butyl ester (D8) (2.52g) in DCM (30ml) was added 4N HCl (5ml) and the mixture was allowed to stir at rt overnight. Evaporation of solvent followed by drying under high vacuum afforded the title compound (D9) as a foam (1.2g).

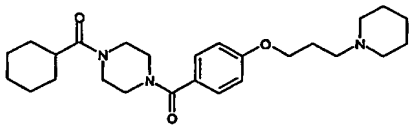
Description 10

(3R,5S)-1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,5-dimethylpiperazine (D10)

(2R,6S)-2,6-Dimethyl-piperazine (0.4g) was dissolved in THF (30 ml) and treated with n-butyl lithium (1.6M solution in hexanes, 4.82ml) under argon. The mixture was stirred at rt for 30min and then 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (1.0g), dissolved in DCM (10ml), was added dropwise. The reaction was stirred for 1h and then evaporated to a minimum and the crude residue purified by column chromatography [silica gel, eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM] to afford the title compound (D10) as a yellow oil (0.65 g).

Example 1

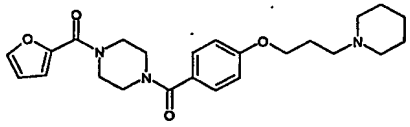
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(1-cyclohexanecarbonyl)-piperazine hydrochloride (E1)



To 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.24g) in DCM (10 ml) was added 1-(cyclohexanecarbonyl)-piperazine (0.155 g) and diethylaminomethyl polystyrene (3.2mmol/g, 0.69g). The mixture was stirred for 16h. The reaction mixture was then loaded directly onto a silica column and eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM. The isolated free base was dissolved in DCM (5ml) and treated with 4N HCl/Dioxane solution (1 ml) with stirring for 10 min. The reaction was concentrated, and the residue co-evaporated with toluene (3 x 10ml) and then dried at 50°C under high vacuum for 16 h to yield the title compound (E1) as a pale solid (0.165 g). MS electrospray (+ion)-442 (MH^+). ^1H NMR δ (DMSO-d6): 9.71 (s, 1H), 7.39 (d, 2H, J=6.84Hz), 7.00 (d, 2H, J=6.84Hz), 4.10 (m, 2H), 3.47-3.25 (m, 10H), 3.16 (m, 2H), 2.90 (m, 2H), 2.55 (m, 1H), 2.19 (m, 2H), 1.82-1.62 (m, 10 H), 1.40-1.16 (m, 6H).

Example 2

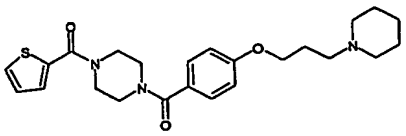
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(2-furoyl)-piperazine hydrochloride (E2)



The title compound was prepared from 4-(3-piperidin-1-ylpropoxy)benzoyl chloride hydrochloride (D3) (0.24g) and 1-(2-furoyl)piperazine (0.12g) using the procedure described for Example 1 and isolated as a pale yellow solid (0.16g). MS electrospray (+ion) 426 (MH^+). ^1H NMR δ (DMSO-d6): 9.80 (s, 1H), 7.84 (s, 1H), 7.43 (d, 2H, J=6.80Hz), 7.03 (m, 1H), 7.02 (d, 2H, J=6.80Hz), 6.63 (m, 1H), 4.11 (m, 1H), 3.72-3.45 (m, 10H), 3.16 (m, 2H), 2.90 (m, 2H), 2.18 (m, 2H), 1.82-1.40 (m, 6H).

Example 3

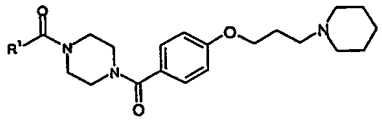
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(thiophen-2-carbonyl)-piperazine hydrochloride (E3)

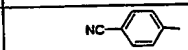
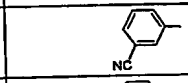
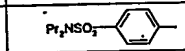
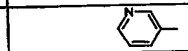
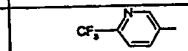
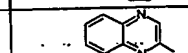
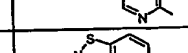
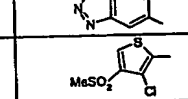
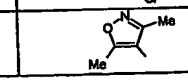


N-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) (0.15g) was stirred with diethylaminomethyl polystyrene (3.2mmol/g, 0.35g) in DCM (10 ml) and thiophen-2-carbonyl chloride (0.057g) added. The reaction was stirred for 16h and then loaded directly onto a silica column, eluting with 0-10% MeOH (containing 10% 0.880 ammonia solution)/DCM. The isolated free base product was then dissolved in DCM (5ml) and treated with 4N HCl/Dioxane solution (1 ml) and stirred for 10 min. The reaction was concentrated, and the residue co-evaporated with toluene (3 x 10ml) then dried at 50°C under high vacuum for 16h to yield the title compound (E3) as a pale yellow solid (0.14g). MS electrospray (+ion) 442 (MH^+). ^1H NMR δ (DMSO-d6): 9.85 (s, 1H), 7.77 (m, 1H), 7.44 (m, 3H), 7.13 (m, 1H), 7.01 (d, 2H, 8.72Hz), 4.10 (m, 2H), 3.70-3.34 (m, 10H), 3.17 (m, 1H), 2.89 (m, 2H), 2.17 (m, 2H), 1.79-1.37 (m, 6H).

Examples 4-18 (E4-E18)

Examples 4 - 18 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) and the appropriate acid chloride using the procedure described in Example 3 and displayed ^1H NMR and mass spectral data that were consistent with structure.

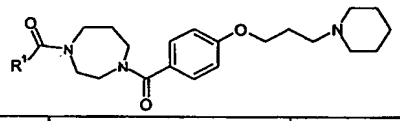


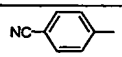
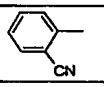
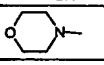
Example No	R^1	Mass Spectrum (ES^+)
E4		$[M+H]^+$ 461
E5		$[M+H]^+$ 461
E6		$[M+H]^+$ 600
E7		$[M+H]^+$ 437
E8		$[M+H]^+$ 505
E9		$[M+H]^+$ 488
E10		$[M+H]^+$ 452
E11		$[M+H]^+$ 494
E12		$[M+H]^+$ 555
E13		$[M+H]^+$ 455

E14		$[M+H]^+$ 427
E15		$[M+H]^+$ 496
E16		$[M+H]^+$ 454
E17		$[M+H]^+$ 496
E18		$[M+H]^+$ 496

Examples 19-21 (E19-E21)

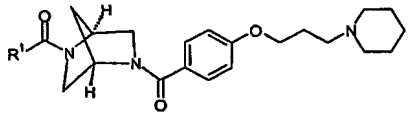
Examples 19-21 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]homopiperazine dihydrochloride (D7) and the appropriate carboxylic acid chloride or carbamoyl chloride following the procedure described for Example 3 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.

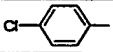
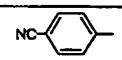


Example No	R^1	Mass Spectrum (ES^+)
E19		$[M+H]^+$ 475
E20		$[M+H]^+$ 475
E21		$[M+H]^+$ 459

Examples 22 and 23 (E22-E23)

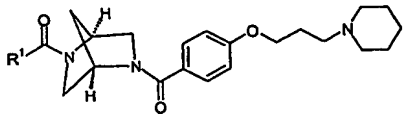
Examples 22 and 23 were prepared from (1S,4S)-2-[4-(3-piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane dihydrochloride (D9) and the appropriate acid chloride following the procedure described for Example 3 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^1	Mass Spectrum (ES^+)
E22		$[M+H]^+$ 483
E23		$[M+H]^+$ 473

Examples 24 and 25 (E24-E25)

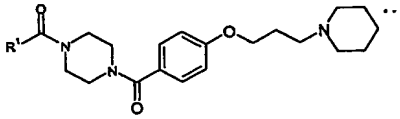
Examples 24 and 25 were prepared from (1S,4S)-2-[4-(3-piperidin-1-ylpropoxy)benzoyl]-2,5-diaza-bicyclo[2.2.1] heptane dihydrochloride (D9) and the appropriate carbamoyl chloride following the procedure described for Example 3, and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^1	Mass Spectrum (ES^+)
E24		$[M+H]^+$ 441
E25		$[M+H]^+$ 457

Examples 26-33 (E26-E33)

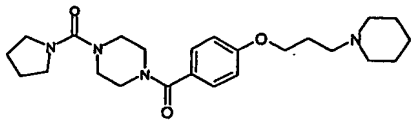
Examples 26-33 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) and the appropriate carboxylic acid chloride using the procedure described in Example 3 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^1	Mass Spectrum (ES^+)
E26		$[M+H]^+$ 402
E27		$[M+H]^+$ 436
E28		$[M+H]^+$ 471
E29		$[M+H]^+$ 471
E30		$[M+H]^+$ 504
E31		$[M+H]^+$ 504

Example 32

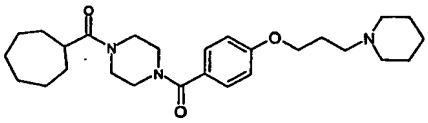
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(pyrrolidine-1-carbonyl)-piperazine hydrochloride (E32)



The title compound (E32) was prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride) (D5) (0.15g) and pyrrolidine-1-carbonyl chloride (0.054 g) using the procedure described in Example 3 and was obtained as a white solid (0.10 g). MS electrospray (+ion) 429 (MH^+). ^1H NMR δ (DMSO-d6): 9.75 (s, 1H), 7.40 (d, 2H, J=8.4Hz), 7.00 (d, 2H, J=8.4 Hz), 4.10 (t, 2H, J=6.0Hz), 3.47 (m, 6H), 3.27 (m, 4H), 3.18 (m, 6H), 2.87 (m, 2H), 2.17 (m, 2H), 1.74-1.39 (m, 10H).

Example 33

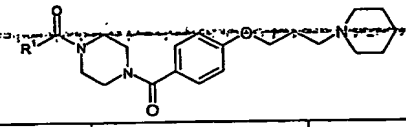
1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-4-(cycloheptanecarbonyl)-piperazine hydrochloride (E33)



1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (0.15g) (D5) was dissolved in DCM (5ml) and diethylaminomethyl polystyrene resin (3.2 mmol/g, 0.465 g) was added, followed by cycloheptane carboxylic acid (0.063g) , HOBT (0.065 g), and EDC (0.092g). The reaction was stirred at rt overnight, then filtered and washed with saturated sodium hydrogen carbonate solution (3x50ml) and brine (50ml). The organic layer was dried (magnesium sulphate) and evaporated to give a crude product, which was purified by column chromatography [silica gel, eluted with 0-10% MeOH (containing 10% 0.880 ammonia solution) in DCM]. The isolated free base was then dissolved in DCM (5ml) and treated with 4N HCl/dioxane solution (1ml) and stirred for 10min. The reaction was concentrated, and the residue co-evaporated with toluene (3x10ml) then dried at 50°C under high vacuum for 16h to yield the title compound (E33) as a pale solid (0.051g). MS electrospray (+ion) 456 (MH^+). ^1H NMR δ (DMSO-d6): 9.55 (s, 1H), 7.40 (d, 2H, J=8.76 Hz), 7.00 (d, 2H, J=8.76Hz), 4.10 (t, 2H, J=9.93 Hz), 3.51 (m, 10H), 3.17 (m, 2H), 2.90 (m, 2H), 2.73 (m, 1H), 2.18 (m, 2H), 1.83-1.66 (m, 9H), 1.44 (m, 9H).

Examples 34-43 (E34-E43)

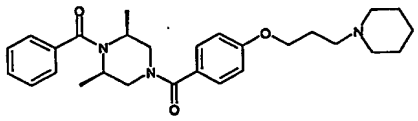
Examples 34-43 were prepared from 1-[4-(3-piperidin-1-ylpropoxy)benzoyl]piperazine dihydrochloride (D5) and the appropriate carboxylic acid using the procedure described in Example 33 and displayed ^1H NMR and mass spectral data that were consistent with structure.



Example No	R^1	Mass Spectrum (ES^+)
E34		$[M+H]^+$ 437
E35		$[M+H]^+$ 451
E36		$[M+H]^+$ 452
E37		$[M+H]^+$ 456
E38		$[M+H]^+$ 498
E39		$[M+H]^+$ 430
E40		$[M+H]^+$ 444
E41		$[M+H]^+$ 464
E42		$[M+H]^+$ 490
E43		$[M+H]^+$ 478

Example 44

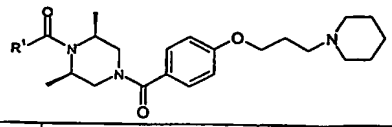
(3S,5S)-1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,5-dimethyl-4-benzoyl-piperazine] hydrochloride (E44)



(3R,5S)-1-[4-(3-Piperidin-1-ylpropoxy)benzoyl]-3,5-dimethylpiperazine (D10) (0.15g) was dissolved in DCM (5ml) and treated with diethyalaminomethyl polystyrene resin (3.2mmol/g, 0.60g) followed by benzoyl chloride (0.053g). The reaction was stirred at rt for 16h and then loaded directly onto a silica column, eluting with 0-10% MeOH (containing 10% 0.880 ammonia solution)/DCM. The isolated free base product was then dissolved in DCM (5ml) and treated with 4N HCl/Dioxane solution (1ml) and stirred for 10min. The reaction was concentrated, and the residue co-evaporated with toluene (3x10ml) then dried at 50°C under high vacuum for 16h to yield the title compound (E44) as a white solid (0.10g). MS electrospray (+ion) 464 (MH^+). ^1H NMR δ (DMSO-d6): 9.74 (1H, s), 7.39 (7H, m), 7.01 (2H, d, J=8.7Hz), 4.40-4.09 (4H, m) 3.47-3.15 (6H, m), 2.92 (2H, m), 2.20-1.28 (10H, m), 1.15 (6H, m).

Examples 45-46 (E45-E46)

Examples 45-46 were prepared from (3R,5S)-1-[4-(3-piperidin-1-ylpropoxy)benzoyl]-3,5-dimethylpiperazine (D10) and the appropriate carboxylic acid chloride using the procedure described in Example 44 and displayed ^{1}H NMR and mass spectral data that were consistent with structure.



Example No	R^1	Mass Spectrum (ES^+)
E45		$[M+H]^+$ 454
E46		$[M+H]^+$ 470

Abbreviations

Boc	tert-butoxycarbonyl
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBT	1-hydroxybenzotriazole
h	hour
DCM	dichloromethane
MeOH	methanol
min	minutes
rt	room temperature
DMSO	dimethylsulfoxide

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was

transformed into competent DH5α *E. coli* host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the *sh ble* gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is

resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10µl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/µl or 50µCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80µl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller. The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

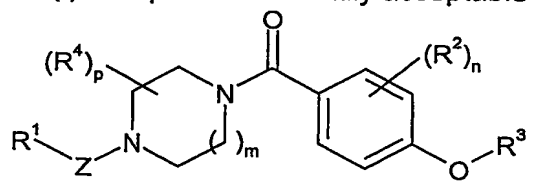
The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

Results

The compounds of Examples E1-E46 were tested in the histamine H3 functional antagonist assay and exhibited pK_b values > 8.0. More specifically, the compounds of Examples 1, 2, 4, 5 and 44 demonstrated pK_b values ≥ 8.5.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents -C_{1-6} alkyl, -C_{1-6} alkylC_{1-6} alkoxy, -C_{3-8} cycloalkyl, aryl, heterocyclyl, heteroaryl, -C_{1-6} alkyl-aryl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, -C_{1-6} alkyl-heteroaryl, -C_{1-6} alkyl-heterocyclyl, -aryl-aryl, -aryl-heteroaryl, -aryl-heterocyclyl, -heteroaryl-aryl, -heteroaryl-heteroaryl, -heteroaryl-heterocyclyl, -heterocyclyl-aryl, -heterocyclyl-heteroaryl or -heterocyclyl-heterocyclyl;

wherein R^1 may be optionally substituted by one or more (eg. 1, 2 or 3) substituents which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, oxo, haloC_{1-6} alkyl, polyhaloC_{1-6} alkyl, haloC_{1-6} alkoxy, polyhaloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonyl, arylsulfonyloxy, aryloxy, arylsulfonamido, arylcarboxamido, aroyl, or a group $NR^{15}R^{16}$, -$CONR^{15}R^{16}$, -$NR^{15}COR^{16}$, -$NR^{15}SO_2R^{16}$ or -$SO_2NR^{15}R^{16}$, wherein R^{15} and R^{16} independently represent hydrogen or C_{1-6} alkyl or together form a heterocyclic ring;

Z represents CO or SO_2;

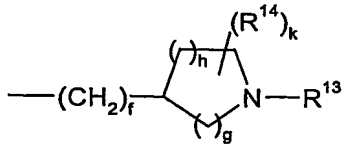
R^2 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

m is 1 or 2;

n is 0, 1 or 2;

p is 0, 1 or 2;

R^3 represents -$(CH_2)_q$-$NR^{11}R^{12}$ or a group of formula (i):



(i)

wherein q is 2, 3 or 4;

R^{11} and R^{12} independently represent C_{1-6} alkyl or together with the nitrogen atom to which they are attached represent an N-linked heterocyclic group selected from pyrrolidine, piperidine and homopiperidine optionally substituted by one or two R^{17} groups;

R^{13} represents C_{1-6} alkyl, C_{3-6} cycloalkyl or -C_{1-4} alkyl-C_{3-6} cycloalkyl;

R^{14} and R^{17} independently represent halogen, C_{1-4} alkyl, haloC_{1-6} alkyl, OH, diC_{1-6} alkylamino or C_{1-6} alkoxy;
f and k independently represent 0, 1 or 2;
g is 0, 1 or 2 and h is 0, 1, 2 or 3, such that g and h cannot both be 0;
R^4 represents C_{1-6} alkyl such that when p represents 2, said R^4 groups may form a bridging group consisting of one or two methylene groups;
or a solvate thereof..

2. A compound according to claim 1 which is a compound of formula E1-E46 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 for use in therapy.

4. A compound according to claim 1 or claim 2 for use in the treatment of Alzheimer's disease.

5. A pharmaceutical composition which comprises a compound according to claim 1 or claim 2 and a pharmaceutically acceptable carrier or excipient.